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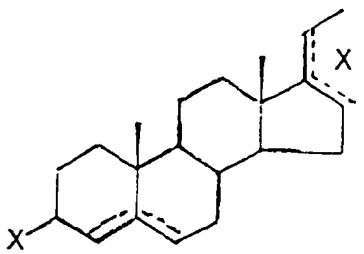
(54) Medicaments for hypolipidemic and hypoglycemic conditions

(57) The invention provides a method of using pregnadienones and pregnadienols represented by the structural formula (I) as shown herein below



I

Wherein X=OH or O or combination thereof and positioning of olefinic bonds are at 4(5); 5(6); 6(17); 17(20) or various combinations and said compounds containing at least one olefinic bond in or on their D-ring for the treatment of hypolipidemic and hypoglycemic conditions in mammals, said method comprising administering an effective amount of the said compounds to the recipient mammals.

EP 1 020 191 A1

Description

Field of the Invention

[0001] This invention relates to the novel use of D-ring unsaturated pregnadienols/ pregnadienones represented by general formula I as shown in the accompanying drawings, possessing both pronounced hypolipidemic and hypoglycemic activities and devoid of androgenic and progestational activities. More particularly this invention relates to the novel use of 3β-hydroxy-pregna-5, 16-dienone an important prototype of this class, represented by the formula (II) as shown in the accompanying drawings, for the treatment of diabetes and pronounced hypolipidemic and hypoglycemic activities.

Background

[0002] High plasma cholesterol and related lipids are known to be one of the factors that predispose an individual to atherosclerosis and thus to myocardial infraction. Diabetes mellitus, which eventually impairs the function of kidneys, eyes, nervous and vascular systems, is quite often associated with lipid disorders. Both hyperlipidemia and diabetes mellitus require long term management and pose problems in choice of pharmacotherapeutic interventions when these conditions manifest together. Though a number of drugs are known separately to treat these conditions, there are a number of side effects associated with them which limit their long term use.

[0003] The most important hypolipidemic drugs available today belong to the statin and fibrate classes [McCarthy, P.A., Med. Res. Rev., 13, 139-59 (1993)] whereas hypoglycemic drugs fall into the category of sulphonylureas, biguanidines and amidines [Wolff, M.E. (Ed), Burger's Medicinal Chemistry Part II, 1045 (1981), John Wiley & Sons, New York]. However, these therapeutic agents are not free of side effects-statins (HMG-CoA reductase inhibitors) the most widely used drugs today which hitherto were thought to be very safe drugs, have exhibited side effects following long term therapy [Carrier, M. et al.; Ann. Thorac. Surg., 57, 353-6 (1994)]. The adverse effects which have become the source of concern, are increases in hepatic transaminases and myopathies [Witztum, J.L., In Goodman & Gilman's The Pharmacological Basis of Therapeutics, eds. Hardman, J. et al., 9th edition, McGraw Hill, New York pp. 875-98, Fukami, M. et al; Res. Exp. Med., 193, 263-73 (1993); Appelkvist, E..; et al.; Clin. Invest., 71 (suppl 8), 597-102 (1993), Wills, R.A. et al.; Proc. Natl. Acad. Sci. (US), 87, 8928-30 (1990)] and carcinogenesis specially breast cancer in subjects undergoing treatment with pravastatin [Braunwald, E.; Scrip, 2117, 33 (1996)); Ciaravino, V. et al.; Mutat. Res.; 353, 95-107 (1995)]. The incidence of myopathy associated with rhabdomyolysis and renal failure is increased subsequent to such treatment [East, C. et al.; N. Engl. J. Med., 318, 47-48 (1998); Pierce L.R. et al.; J. Am.Med. Assoc., 265, 71-75 (1990)]. Also, these HMG-CoA inhibitors block mevalonate production which occurs at an early stage in cholesterol synthetic pathway. Mevalonate is a common precursor for all isoprenoids such as ubiquinones (Co-enzyme Q-10), the dolichols, isopentenyl t-RNA etc. Therefore, long term blockade of mevalonate synthesis leads to Q-10 deficiency. Serum Co-enzyme Q-10 is important for cardiac function {Laaksonen, R. et al., Eur. J. Clin. Pharmacol. 46,313-7 (1994); Bargossi, A.M. et al; Int.J. Clin. Lab. Res., 24, 171-6 (1994)]. The commonest side-effects of fibrates and particularly clofibrate therapy are gastrointestinal upsets including nausea, vomiting, diarrhoea, dyspepsia, flatulence and abdominal discomfort [Oliver ,M. F. et al.; Br. Heart J., 40, 1069-1118 (1978)]. Elevated creatine phosphokinase concentration during clofibrate therapy may be associated with a syndrome of muscle pain and weakness. Large-scale long-term studies have demonstrated an increased incidence of cholecystitis, gallstones and sometimes pancreatitis in patients receiving clofibrate and some studies have indicated cardiovascular disorders [The coronary Drug Project Research Group; N. Engl. J. Med., **296**, 1185-90 (1977)]. The unexpected finding of an increased mortality rate in patients taking clofibrate in the WHO study produced serious concern over the long-term safely of clofibrate and ultimately led to its withdrawal in many countries [Oliver, M. F. et al ; Lancet, **ii**, 600-604 (1984)].

[0004] The adverse effects of biguanidine antidiabetic agents include gastro-intestinal disturbances like diarrhoea and lactic acidosis [Paterson, K. R. et al.; Adverse Drug React Acute Poisoning Rev., 3, 173-82 (1984)]. With sulphonylureas the commonly associated adverse effects are hypoglycemia, gastrointestinal disturbances, hypersensitivity and vascular complications [Paice, B.J. et al., Adverse Drug React. Acute Poisoning, **4**, 23-26 (1985)]. As diabetes and hyperlipidemia are quite commonly manifesting together, it would be of great clinical benefit if the same compound could have both these activities together because the available drugs are not free of toxic effects and neither data regarding toxic manifestations are available when drugs for two clinical conditions are mixed together.

[0005] Two approaches currently being pursued in search of drugs with hypolipidemic and hypoglycemic activities together. The first approach emerged during detailed study of antihypertensive action of adrenergic receptor modulators. The study revealed that α_1-adrenergic blockers (particularly Doxazosin and Prazosin) [Lithell, H.O. ; J. Hypertens, **15** (Suppl 1), S 39-42 (1997); Poliare,T. et al.; Diabetologia, **31**, 415-420 (1988); Anderson, P.E. et al.; Am. J. Hypertens, 9, 323-333 (1996)] and β_3-adrenergic agonist (BTA-243, BRL-37344, CGP 12177, CL 316243 [Arch, J. R. S. et al.; Med. Res. Rev., **13**, 663-729 (1993); Largis, E. E. et al;. Drug Dev. Res.. **32**, 69-76 (1994)] also affect plasma lipoprotein

metabolism and increase insulin sensitivity; As a result such antihypertensive drugs exhibit lipid lowering and hypoglycemic actions together, α_1-adrenergic receptor blockers, however have the inherent limitations of causing orthostatic hypotension and syncope [Matyus, P.; Med. Res. Rev., **17**(6), 523-35 (1997)]. The essential requirement of β_3-agonist for antiobesity and antidiabetic actions is the need for high selectivity for β_3-adrenoceptor, Any substantial β_1- or β_2-agonism would likely cause increased heart rate and muscle tremor respectively which are unacceptable in a drug which could be administered on long term basis [Connacher, A . A. et al.; Brit. Med. J., **296**, 1217-20 (1988); Mitchell, T. H. et al; Int. J. Obesity., **13**(6), 757-66 (1989)]. The second line of approach for dual activity came into light during the study of anti-oxidant property of drugs. There have been many reports describing relationships between peroxidation and diseases such as diabetes mellitus, atherosclerosis and myocardial ischemia in terms of radical oxidation. Troglitazone, an antioxidant drug has been developed as an oral hypoglycemic agent which enhances the action of insulin in peripheral tissues and liver besides its hypolipidemic effects. However, troglitazone is also not free of major side effect causing liver damage. The drug, troglitazone, has been implicated in 35 cases of liver disease leading to one transplant and one death [Warner-Lambert; Chem. & Ind., No.**22.** 897 (1997)]. Thus to the best of our knowledge no class of compound is yet available which has both effects together as the main action and have fair safety margin.

[0006] We, in early eighties started our work for search of such compounds which have effect on endogenous transportation of lipids and glucose rather than interfering with exogenous transportation. Our research was mainly based on secondary metabolic actions of progesterone.

[0007] Progesterone, apart from its classical hormonal action on the reproductive system, is known to modulate lipid, carbohydrate, insulin and protein metabolism. The rise in the level of progesterone in the first trimester of pregnancy causes hyperphagia, pancreatic islet hypertrophy, hyperinsulinemia and body fat and glycogen deposition, when the metabolic demands of the fetus are very low. However, in the latter half of pregnancy, although the progesterone levels are still high, the carbohydrate, lipid and protein reservoirs shift into circulation to meet the needs of the growing fetus. [Kalkhoff, R.K.; Am. J. Obstet. Gynecol., **142**, 735-38 (1982)].

[0008] Progesterone thus, having actions both on the reproductive and the metabolic systems, seemed to offer the possibility of dissociating these two biological activities by structural modifications. The experience of the development of second generation progestins supported this contention. The first generation progestins such as levonorgestrel exhibited undesirable pharmacologic effects like alteration in carbohydrate and lipoprotein metabolism, weight gain and hypertension, which was shown to be related to their intrinsic androgenic/anabolic activity and ability to bind with androgen receptors. The androgenic affinity has been attributed to C-17 hydroxy functionality which makes these molecules resemble androgens. In recently discovered second generation progestins such as gestodene and 3-keto-desogestrel, an additional olefinic bond either in C- or D- ring brought a dramatic decrease in their affinity to androgen receptors (Table 1). As a result these compounds have a very high order of progestational effect with practically no androgenic activity and did not cause hyperlipidemia [London, R.S.; Obstetrical & Gynocological Survey, **47**, 777-81 (1992)].

Table 1.

Relative Binding Affinity of Contraceptive Progestins for Progesterone and Androgen receptors			
	Progestin Receptor Binding Affinity	**Androgen Receptor Binding Affinity**	**Selectivity Index* (A/P ratio)**
Progesterone	1.00	0.005	93
Levonorgestrel	5.41	0.220	11
3-Keto-desogestrel	8.6	0.120	33
Gestodene	9.21	0.154	28

* The higher the selectivity index, the greater the separation between the dose needed to achieve the desired progestational effect and the dose associated with the undesired androgenic effect [Collins, D.C. Am. J. Obstet. Gynecol. **170**, 1508-13 (1994)].

Objects of the invention

[0009] It is an object of the invention to explore the possibility of designing pregnadienones which while preserving the ability to modulate lipid and carbohydrate metabolism would not have any progestational effect. It would be pertinent to point out that earlier, the applicants had isolated a D-ring modified pregnenolone, named Gugulsterone represented by formula (9) as shown in Table 2, from guggul resin obtained from *Commiphora mukul,* which had potent hypolipidemic effect without any progestational effect [Arya, V.P.; Drugs Fut. 13, 618 (1998)].

[0010] It is another object of the invention to explore the possibility of dissociating the hypolipidemic and insulin sensitizing activities of progesterone from its hormonal actions. Accordingly, the applicants focussed their attention to

prepare and investigate analogues/prototypes with additional substituents in ring-D of pregnadienones.

Brief description of the accompanying drawings

[0011]

Figure 1 (I) represents the structural formula of compounds belonging to the class of pregnadienones and pregnadienols and

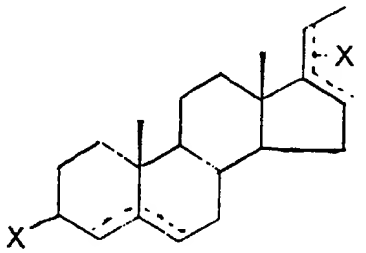
Figure 1 (II) represents the structural formula of 3β-hydroxypregna-5, 16-lien-20-one

Figure 2 represents the structural formulae of hormones.

Summary of the invention

[0012] In accordance with the above objectives, the applicant's present invention relates to a method of using D-ring unsaturated pregnadienones represented by structural formula I which causes significant fall of serum cholesterol, triglycerides, LDL-cholesterol and glucose with mild increase in HDL-cholesterol, said method comprising administration of effective amounts of said compounds of formula (I) to mammals. The compounds possess fair safety margin having antioxidant and cardio protection activities.

[0013] The invention also provides a method of treatment of hypolipidemic and hypoglycemic conditions which comprises administration to a recipient a therapeutic composition comprising a pharmaceutically effective amount of compound D-ring unsaturated preganadienones represented by the general formula I as shown hereinbelow and in the accompanying drawings:



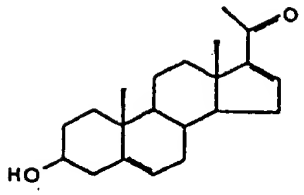
I

Wherein X= OH or O or combination thereof and positioning of olefinic bonds are at 4(5); 5(6); 16(17); 17(20) or various combinations

Detailed description of the invention

[0014] The present invention concerns methods for lowering serum cholesterol, triglycerides and glucose levels in subjects with obesity and diabetic conditions or prophylactically holding in check the symptoms of such a disease state.

[0015] In particular, the applicants, during their study, have observed that the pregnadienone, 3β-hydroxypregna-5, 16-dien-20-one represented by the structural formula (II) shown hereinbelow and in the accompanying drawings is useful for the treatment of hypolipidemic and hypoglycemic conditions.



II

[0016] Accordingly, the invention provides a method of using compounds represented by the structural formula (I) as shown in the accompanying drawings, containing at least one olefinic bond in or on their D-ring for the treatment of hypolipidemic and hypoglycemic conditions in mammals, said method comprising administering an effective amount of the said compounds to recipient mammals.

[0017] In one embodiment, the compounds of formula (I) are administered in the form of tablets, capsules or injectibles.

[0018] In another embodiment, the compounds of formula (I) are characterised as pregnadienones and pregnadienols.

[0019] In yet another embodiment, the most preferred compound belonging to the family of preganienones and pregnadienols represented by formula (I) is 3β-hydroxy-pregna-5,16-dien-20-one, which is represented by the structural formula (II) as shown in the accompanying drawings.

[0020] In a further embodiment, the compounds of formula (I) are optionally administered to the recipient mammal as an admixture with conventional anti-platelet, anti artherosclerotic, hypolipoproteinic and antidiabetic drugs.

[0021] In still another embodiment, the compounds of formula (I) are essentially free of side effects associated with conventional hypolipidemic and hypoglycemic drugs.

[0022] In an embodiment, the compounds of formula (I) exhibit cardioprotective, anti-diabetic, anti-artherosclerotic and anti-oxidant properties.

[0023] Further, the invention provides a method of treatment of hypolipidemic and hypoglycemic conditions in mammals, which comprises administration to a recipient, a therapeutic composition comprising an effective amount of compound of formula (I) with conventional carriers.

[0024] In an embodiment, the recipient mammals are selected from the group comprising rats, human beings, rhesus monkeys and rabbits.

[0025] In another embodiment, the conventional carriers are selected from anti-platelet, anti-artherosclerotic, hypolipoproteinic and anti-diabetic drugs.

[0026] In yet another embodiment, the said compounds of formula (I) essentially contain an olefinic bond in or on their D-ring.

[0027] In a further embodiment, the compounds of formula (I) are essentially free of androgenic, progestinal and side effects.

[0028] In still another embodiment, the therapeutic composition is administered in the form of tablets, capsules and injectibles.

[0029] In another embodiment, the said preganadienones and preganadienols exhibit cardio protective, antidiabetic, antialtheroselerotic and antioxidant properties.

[0030] In yet another embodiment, the said preganadienones and pregnadienols of formula I essentially contain olefinic bond in one of the D-rings.

Methods of synthesis/production

[0031] 3β-Hydroxy pregna-5, 16-dien-20-one The methods of synthesis are essentially known in the literature/can be obtained from diosgenin by chemical degradation [G. Rosenleranz "History of Steroids", Steroids, 57, 409 (1992)]. Although, it was later isolated from Veratrum Grandiflorum [Kanko, K. et al; Phytochemistry, 12 1509 (1973)] but yield is too low to be of any practical value. Oppenauer oxidation of **2** with aluminium-*iso*propoxide and cyclohexanone in toluene produces 4,16-dienpregna-3,20-dione [16-dehydroprogesterone, (**3**)]. The C-16(17)olefinic bond in **1** is selectively reduced with Pd-C in diethylether at very low hydrogen gas pressure. The resultant product **4** on basic hydrolysis furnishes 5. The procedure of Benn and Dodson (J. Org. Chem. **29**, 1142 (1964)] was followed for the preparation of Gugulsterone (9). The reduction of 16-DPA (**1**) with lithium aluminium hydride produces diol **6** which after Sigmatropic rearrangement in presence of p-toluenesulphonic acids acetic acid and acetic anhydride produces the diacetate 7. Basic hydrolysis of the diacetate 7 followed by Oppenauer oxidation furnishes an 80 : 20 mixture of E&Z- Gugulsterone

(9).

5. BIOLOGICAL ACTIVITY

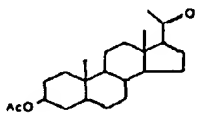
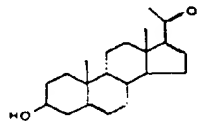
5.1 Hypolipidemic Activity

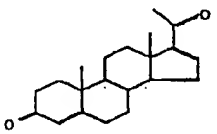
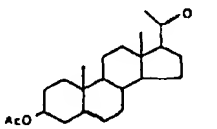
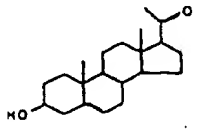
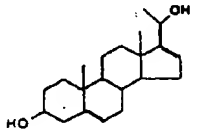
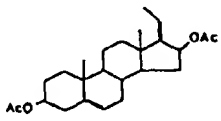
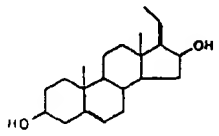
[0032] The primary hypolipidemic effect of these compounds were established in triton induced hyperlipidemia in Charles Foster rats. The compounds which exhibited significant lipid lowering effect in this model were then evaluated for their hypolipidemic effect in normal, and diet induced hyperlipidemic rats, rabbits and rhesus monkeys.

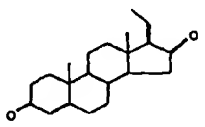
5.1.1. Hypolipidemic Activity In Triton Treated Rats

[0033] The cholesterol lowering effect of some representative compounds of pregrenadienols and - pregrenadienones as compared to clofibrate and gugulsterone in triton treated Charles Foster rats is described in Table-2

Table-2 : Cholesterol lowering effect of pregnane compounds as compared to Clofibrate in Triton treated rats

Compd. No.	Compound	Structure	Dose (i.p.) mg/kg	% Change S. Chol.
1	3ß-Acetoxypregna-5,16-dien-20-one (16-DPA)		50	-43
2	3ß-Hydroxypregna-5,16-dien-20-one		50	-46

3	4,16-Dienpregna-3,20-dione		50	-13
4	3ß-Acetoxypregna-5-en-20-one		100	-12
5	3ß-Hydroxypregna-5-en-20-one		100	-09
6	5,16-Dien-pregnane-3,20-diol		50	-10
7	5,17(20)-Dienpregna-3,16-diol-diacetate		50	-33
8	5,17(20)-Dienpregna-3,16-diol		50	-31

9	Gugulsterone		50	-44
10	Clofibrate		200	-15

[0034] The results showed that of the compounds tested, the highest effect was exhibited by 16-DPA (1) and its 3-des-acetyl analog **2** comparable to gugulsterone (**9**), and that the removal of double bond in ring D of **1** or **2** almost abolished the effect.

5.1.2 Hypolipidemic Activity of 3β-Hydroxypregna-5,16-dien-20-one (2) in Normal Rats

[0035] In normal rats, 3β-hydroxypregna-5,16-dien-20-one (2), at 50 mg/kg produced a significant lowering of serum cholesterol and triglycerides as describe in Table-3 below. The animals did not develop any tolerance to the compound even after administering for 30 days.

Table 3.

Hypolipidemic activity of 3β-Hydroxypregna-5,16-dien-20-one (2) in normal rats					
Treatment	**Serum Cholesterol (mg%)**		**%Fall**	**Serum Triglycrides (mg%) 30 Days**	**% Fall compared to control**
	0 Days	**30 Days**			
2(50mg/kg) (8)	71.5±1.8	43.2±2.9	40 40	42.0±2.8	35
Clofibrate (50 mg/kg) (6)	82.3±3.3	53.2±2.0	36	47.3±3.2	28
Normal saline (control) (6)	83.3±3.1	80.1±1.4	-	65.2±2.9	-
Mean values ± SD. Figure in parenthesis represent number of animals.					

5.1.3 Hypolipidemic Activity in Diet Induced Hyperlipidemic Rats

[0036] Twenty three normal male rats average weight 110-120 g were taken for study and were divided into four groups.Group I: animals recived special diet and 3β-hydroxypregna-5, 16-dien-20-one (**2**) 50 mg/kg p.o. in 1% gum acacia. Group II: animals received 3β-hydroxypregna-5, 16-dien-20-one (2), 100 mg/kg p.o. in 1% gum acacia and special diet. Group III:animals received special fat diet and 1% gum acacia and served as control. Group IV: animals were fed with stock diet and served as normal control. All animals were sacrificed at tile end of 36 days. Blood was drawn from the tail at 10 days and from the aorta at the time of sacrifice for estimation of serum cholesterol, triglycerides and HDL-cholesterol. LDL-cholesterol was calculated as described.
[Roschlau.P. In: Methods of Enzymatic Analysis 4th ed., H.U. Bergmeyer. Ed (Academic Press. New York) 1975 p 1890; Wahlefield, W.A. In: Methods of Enzymatic Analysis, 4th ed.; H.U. Bergmeyer, Ed.(Academic Press, New York) 1974 p 1831.]

Results

[0037] Animals treated with 3β-hydroxypregna-5, 16-dien-20-one (**2**), at 50 and 100 mg/kg showed a significant lowering in serum cholesterol by 31 and 59%, triglycerides by 55 and 62%. LDL-cholesterol by 27 and 74% respectively (Table - 4 & 5).

5.6. PROGESTATIONAI AND ANTIPROGESTATIONAL ACTIVITY

[0049] The relative affinity of compounds for cytoplasmic progesterone receptors present in human breast tumour cells (MCF-7) were estimated and compared with 16-ethyl-21-hydroxy-19-norpregna-4-ene-3,20-dione (Org 2058). The experiments conducted revealed that the compounds 2,3 and 5 have no or only negligible binding affinity.

[0050] The progestational activity was also tested *in vivo* by Clauberg assay method. The degree of endometrial proliferation was estimated on the McPhail scale where 3' or 4' was considered as a full progestational effect, 3β-Hydroxypregna-5,16-dien-20-one (**2**) did not exhibit any activity even at 200 mg/kg dose, whereas progesterone showed, as expected marked progestational activity even at 50 mg/kg.

Claims

1. Use of a compound represented by the structural formula (I) as shown in the accompanying drawings, containing at least one olefinic bond in or on their D-ring in the manufacture of a medicament for the treatment or prophylaxis of a hypolipidemic and/or hypoglycemic condition.

2. Use of a compound represented by the structural formula (I) as shown in the accompanying drawings, containing at least one olefinic bond in or on their D-ring in the manufacture of a medicament for the treatment or prophylaxis of a diabetic condition.

3. Use of a compound represented by the structural formula (I) as shown in the accompanying drawings, containing at least one olefinic bond in or on their D-ring in the manufacture of a medicament for lowering serum cholesterol, triglyceride and/or glucose levels in a subject with obesity or a diabetic condition.

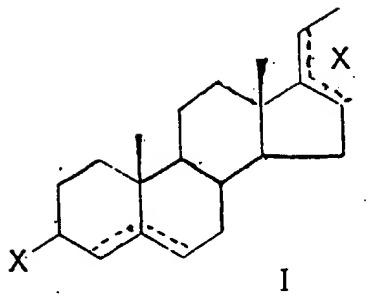
4. Use as claimed in any of claims 1 to 3, wherein the compound of formula (I) is characterised as a pregnadienone or pregnadienol.

5. Use as claimed in any of claims 1 to 4, wherein the compound of formula (I) is 3β-hydroxy-pregna-5,16-dien-20-one, which is represented by the structural formula (II) as shown in the accompanying drawings.

6. Use as claimed in any of claims 1 to 5, wherein a compound of formula (I) is optionally administered as an admixture with one or more other therapeutic agents selected from anti-platelet, anti-artherosclerotic, hypolipoproteinic and antidiabetic drugs.

7. Use as claimed in any of claims 1 to 5 wherein the medicament is in the form of a tablet, capsule or injectible.

8. A compound of formula (I) for use in the treatment of a hypolipidemic and/or hypoglycemic condition.



I

Figure 1 (I)

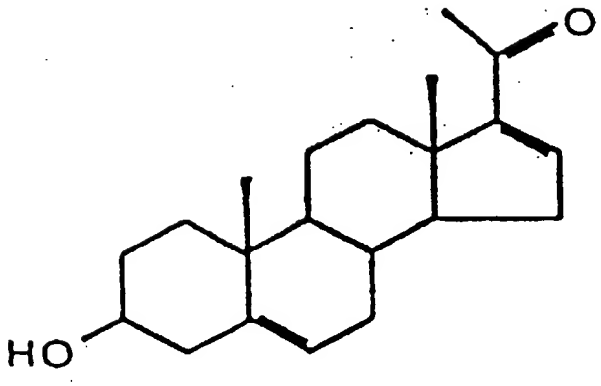
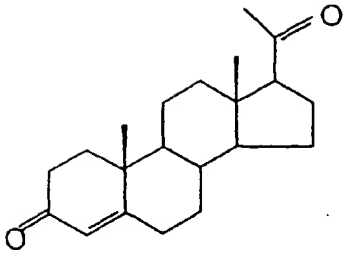
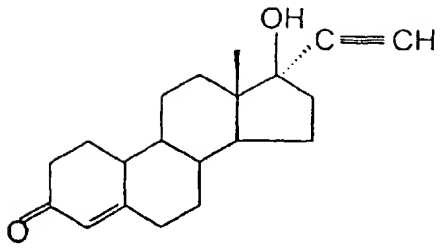


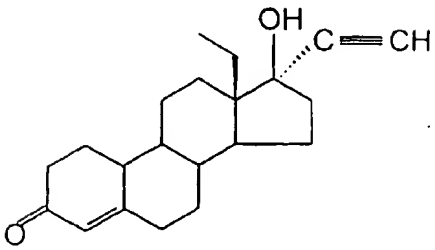
Figure 1 (II)



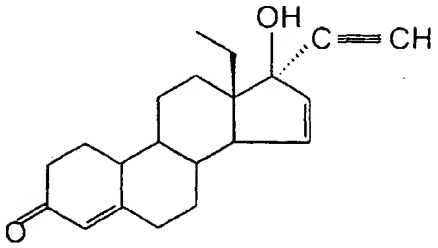
PROGESTERONE



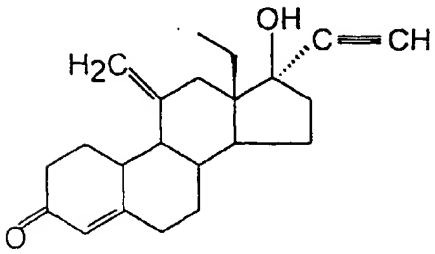
NORETHISTERONE



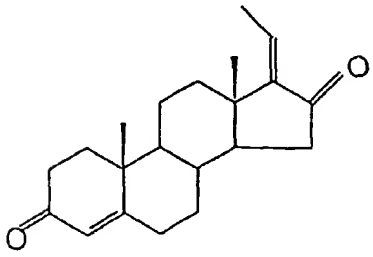
LEVONORGESTREL



GESTODENE



3-KETODESOGESTREL



GUGULSTERONE

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 30 2556

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
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